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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,975	01/10/2006	Wolfgang Stahle	MERCK-3118	7301

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EXAMINER	
CHENG, KAREN	
ART UNIT	**PAPER NUMBER**
1626	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/563,975	STAHLE ET AL.	
	Examiner	Art Unit	
	Karen Cheng	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 1/10/06.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-9 are currently pending in the instant application.

Priority

The application is a 371 of International Application No. PCT/EP04/06630, filed on 06/18/2004, which claims the benefit of foreign priority under 35 U.S.C. 119, to German Application No. 103 31 723.6, filed on 07/11/2003.

Information Disclosure Statement

Applicant's Information Disclosure Statement filed on 01/10/06 has been considered. Please refer to Applicant's copies of the 1449 submitted herewith.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 5 and 8 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd. App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131,149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-6 and 8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The nature of the invention

The nature of the invention is directed to the use of compounds of formula I for the preparation of pharmaceutical composition(s) that can be used for the treatment and/or prophylaxis of diseases influenced by kappa agonists, including irritable bowel syndrome.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat or prevent diseases influenced by kappa agonists such as irritable bowel syndrome). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that that contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any preventive regimen on its fact.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. The burden of enabling one skilled in the art to prevent diseases influenced by kappa agonists, such as irritable bowel syndrome would be much greater than that of enabling the treatment of diseases influenced by kappa agonists, such as irritable bowel syndrome. In the instant case, the specification does not provide guidance as to how one skilled in the art would accomplish the objective of preventing diseases influenced by kappa agonists, such as irritable bowel syndrome. Nor is there any guidance provided as to a specific protocol to be utilized in order to show the efficacy of the presently claimed active ingredients for preventing diseases influenced by kappa agonists, such as irritable bowel syndrome.

Specifically, it is highly unlikely, and the Office would require experimental evidence to support the contention that the claim specified could actually prevent diseases influenced by kappa agonists, such as irritable bowel syndrome by simply administering, by any method, a therapeutically active amount of the claim specified agents. The specification fails to enable one of ordinary skill in the art to practice the presently claimed method for preventing diseases influenced by kappa agonists, such as irritable bowel syndrome.

"To prevent" actually means to anticipate or counter in advance, to keep from happening etc. (as per Webster's II Dictionary) and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compositions can be administered to order to have the "prevention" effect. There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with diseases influenced by kappa agonists, such as irritable bowel syndrome in general. Since applicants "preventive" assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits.

Applicants have not provided any competent evidence or disclosed test results that are highly predictive for the pharmaceutical use of preventing any disease induced by kappa agonist receptors, including irritable bowel syndrome for a human being or other mammal. Hence, one of skill in the art is unable to fully predict possible preventive results from the administration of the claimed compound due to the absence of convincing evidence that said composition has an effect on mammals. No test

results are disclosed in the specification that give guidance as to the actual effect of the compound on any mammal.

According to the National Digestive Diseases Information Clearinghouse, medications used to relieve symptoms of irritable bowel syndrome include antidepressants or antispasmodics, and the medications Donnapine, Librax, Lotronex and Delnorm. There is no mention of the action of the compounds on the kappa receptor, which are expressed in the central nervous system. Simonin *et al* demonstrate that there is a lack of definitive proof of the role of the kappa-opioid receptor in health and disease (p. 312, column 2, paragraph 1). The exact mechanisms of kappa opioid receptor is still being studied and characterized as well as different receptor sub-types. Additionally the numerous challenges in treating irritable bowel syndrome (IBS) including the lack of a realistic animal model of IBS, lack of thorough understanding of mechanisms controlling gut function in health and functional GI diseases, seemingly protean manifestations of IBS, lack of specificity of symptoms, overlap of functional GI disorders with other conditions that require different management, lack of generally applicable methods to evaluate pathophysiology in clinical practice, uncertainty of brain's role in disease, lack of consensus on optimal experimental and trial designs for IBS, and difficulties associated with treating an individual with multiple pharmacological therapeutics (see Camilleri) make the development of pharmaceutical treatments difficult. Although promising results are associated with a kappa-opioid agonist, there has not been an actual drug targeting a kappa receptor developed and used for treatment of irritable bowel syndrome.

The amount of direction or guidance present and the presence or absence of working examples

The specification fails to provide any examples of the effect of the compound on mammals in disease states induced by kappa agonist receptors including irritable bowel syndrome. It fails to provide test results to substantiate the use of a compound of formula I to treat any disease.

The breadth of the claims

The instant breadth of the rejected claims is broader than the disclosure, specifically, the instant claims include treatment and prevention of disease induced by kappa agonist receptors, including irritable bowel syndrome but the specification does not provide evidence of the effect of any of the claimed compounds on any disease states.

The quantity or experimentation needed and the level of skill in the art

It would require undue experimentation of one of ordinary skill in the art to ascertain the effectiveness of the compound in the treatment or prevention of any disease induced by kappa agonist receptors, including irritable bowel syndrome. Factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant claims. The present state of the art is that studies on the kappa opiate receptor, its subtypes, and role in human disease are still being conducted. There is a lack of convincing and substantial evidence linking the kappa opiate receptor to disease states, including irritable bowel syndrome. In view of the breadth of the claims, the

breadth of the claims, the chemical nature of the invention and unpredictability of treatment or prevention of any disease induced by kappa agonist receptors, including irritable bowel syndrome, and the lack of working examples regarding the activity as claimed, one skilled in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in cope with the claims.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

In consideration of the Wand factors, it is apparent that undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue. Therefore, claims 5-6 and 8 are rejected under 35 U.S.C. § 112, 1st paragraph.

Claim Rejections - 35 USC § 112 – 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5 and 8 provide for the use of compounds of the formula I, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it

merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1-9 recite the limitation "pharmaceutically usable derivatives" or "pharmacological usable derivatives." The specification fails to limit and clearly delineate what can be considered a "derivative". According to Hackh's chemical dictionary, "derivative" is defined as a compound, usually organic obtained from another compound by a simple chemical process or an organic compound containing a structural radical similar to that from which it is derived (Hackh's chemical dictionary, 1972). Thus, "pharmaceutically usable derivatives" of the compounds of Claims 1-9 are not defined in the claims so as to know the metes and bounds of the claims. Therefore, Claims 1-9 are indefinite. This rejection can be overcome by deleting the phrase "pharmaceutically usable derivatives."

Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1-9 recite the limitation "exclusively mixtures thereof in all ratios." The specification fails to limit and clearly delineate what can be considered an "exclusively mixtures in all ratios". Thus, "exclusively mixtures thereof in all ratios" of the compounds of Claims 1-9 are not defined in the claims so as to know the metes and bounds of the claims. Therefore, Claims 1-9 are indefinite. This

rejection can be overcome by deleting the phrase "exclusively mixtures thereof in all ratios."

Claims 3, 5-6 and 8-9 recite the limitation "compound of the formula IA" in the claims. There is insufficient antecedent basis for this limitation in the claims as a compound of formula IA is not found in claim 1, which claims 3, 5-6 and 8-9 all depend on. Applicant is advised to delete the phrase compound of the formula IA from these claims in order to overcome this rejection.

Claim Objections

Claim 9 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 6. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim 7 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 1. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). A compound's intended use as a medicament does not further limit the claim.

Objections: Content of Specification

The specification does not incorporate cross reference to related applications. The specification should contain the following sections below, as applicable:

b) Cross-References to Related Applications: See 37 CFR 1.78 and MPEP § 201.11.

Conclusion

A search was made of the prior art, and the closest art was found in US Pat No. 5,232,978 whereby a similar compound that has an alkyl chain in place of the mono- or bicyclic aromatic or non-araomatic carba- or heterocyclic ring system (substituent A) is disclosed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Cheng whose telephone number is 571-272-6233. The examiner can normally be reached on M-F, 9AM to 5:30PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571)272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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